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Synthesis of 2-(5-azido-5-deoxy-β-D-ribofuranosyl)-4-methyl-5-nitro-1,2,3-triazole

Geetha Banda, D Srinivasulu, V Ugandhar & I E Chakravarthy*

Department of Chemistry, Sri Krishnadevaraya University Post Graduate Centre, Kurnool 518 002, India

E-mail: iechakra@yahoo.com

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The synthesis of 2-(5-azido-5-deoxy-β-D-ribofuranosyl)-4-methyl-5-nitro-1,2,3-triazole has been accomplished in 5 steps starting from D-ribose.

Keywords: D-Ribose, nucleosides, 5-nitro-4-methyl-1,2,3-triazole, 2-(5-azido-5-deoxy-β-D-ribofuranosyl)-4-methyl-5-nitro-1, 2, 3-triazole

IPC Code: Int. Cl.[8] C07D

Showdomycin **1** and pyrazomycin **2**[1] are some of the C-nucleoside antibiotics of D-ribose that inhibit uridine monophosphate kinase and uridine phosphorylase. There has been considerable effort on the synthesis of corresponding *N*-nucleosides[2] as their synthetic analogues were found to have broad spectrum of action against RNA and DNA viruses. Therefore, it is evident that nucleoside derivatives of five-membered heterocyclic rings are of considerable interest as compounds of potent biological activity. 1,2,4- and 1,2,3-triazole containing nucleoside analogues resemble the natural pyrimidine nucleosides in a variety of biochemical systems[3] and were earlier synthesized by cycloaddition of various glycosyl azides with substituted acetylenes[4]. Modifications in the glycosyl and triazole moieties of these nucleosides were carried out for the study of structure-activity relationships. Prompted by the activity of triazole attached to D-ribose nucleosides, the synthesis of a new nucleoside 2-(5-azido-5-deoxy-β-D-ribofuranosyl)-4-methyl-5-nitro-1,2,3-triazole **3** (**Figure 1**) from D-ribose was carried out.

Direct fusion in presence of mild acid catalyst has been found to be one of the best methods for the synthesis of triazolyl nucleosides. *Bis*-(*p*-nitrophenyl) hydrogen phosphate has been reported[5] earlier as the best catalyst for the direct fusion of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose with purines, pyrimidines and 1,2,3-triazoles. In order to synthesize target molecule **3**, D-ribose was converted into 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **4** in very good yield using a slightly modified procedure from the one reported in the literature[6]. The other heterocyclic moiety, 5-nitro-4-methyl-1,2,3-triazole **5** was prepared from trinitropropane and sodium azide in 28% yield[7].

Lewis acid catalysts have been earlier used for coupling reactions by Baker[8a] and Furukawa[8b] for the synthesis of purine nucleosides. However, the use of these catalysts to couple the substituted triazole with ribose derivative gave a complicated mixture. The direct fusion of sugar **4** with 1,2,3-triazole **5** in presence of catalytic amounts of *p*-toluene sulphonic acid or *bis*-(*p*-nitrophenyl) hydrogen phosphate at 130°C under vacuum for 15 min gave an oil, which was shown by thin layer chromatography (TLC) to be a mixture of unreacted starting materials and coupled products (**Scheme I**). The major compound was characterized as 2-(2′, 3′, 5′-tri-O-benzoyl-β-D-ribofuranosyl)-5-nitro-4-methyl-1,2,3-triazole **6** and the minor as 1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-

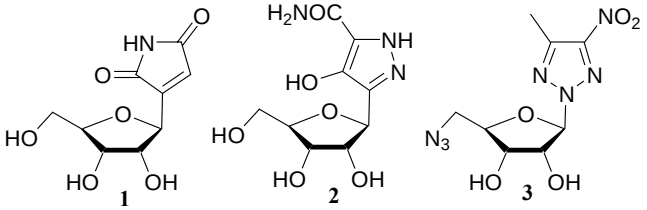
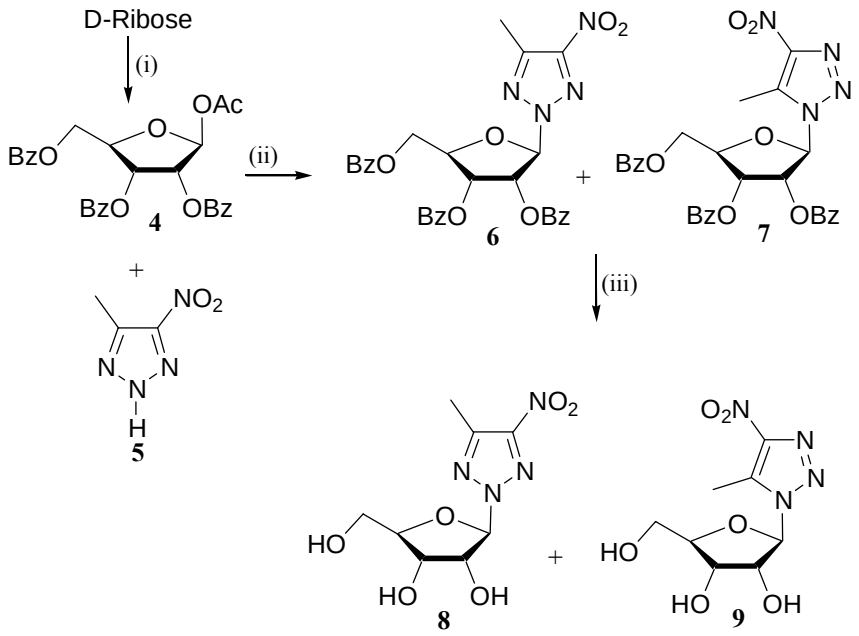


Figure 1



Reagents and conditions: i) BzCl, Py, 95°C, 1 h. 2. Ac_2O, BF_3-Et_2O, 0°C-rt, 1 h. ii) **4** and **5**, PTSA (cat.), 130-135°C, 15 min. iii) NaOMe (cat.), MeOH, RT, 12 h.

Scheme I

4-nitro-5-methyl-1,2,3-triazole **7** based on the literature precedents[2]. The inseparable mixture of **6** and **7** was deacylated by Zemplen method[9] with sodium methoxide in methanol to afford the corresponding deacylated nucleosides **8** and **9** in 87% yield. Repeated chromatographic purification of the crude mixture gave pure **8** and **9**. Compound **8** was characterized by the ^{1}H NMR spectrum from the appearance of anomeric proton at δ 5.98 (d, 1H) and methyl protons of triazole at δ 2.57 (s, 3H) and by ^{13}C NMR spectra from the appearance of anomeric carbon at δ 98.9. Compound **9** was also characterized by ^{1}H NMR from the appearance of anomeric proton at δ 6.30 (d, 1H).

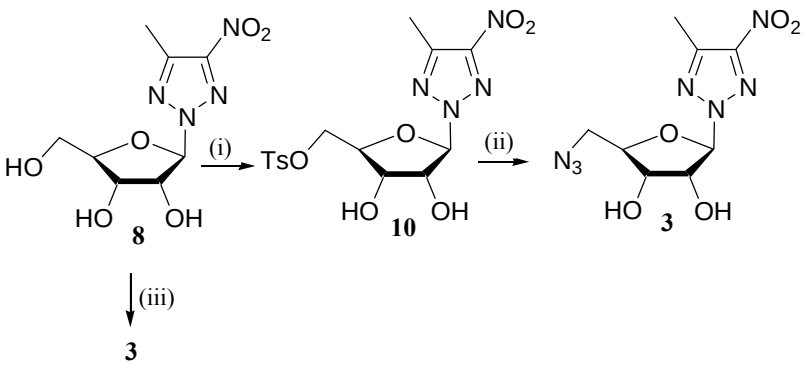
Mitsunobu reaction[10] of **8** with diethyl azodicaroboxylate (DEAD), triphenyl phosphine and diphenylphosphoryl azide (DPPA) in THF gave a mixture and isolation of the pure compound **3** was unsuccessful. Alternatively, compound **8** was converted into its 5-O tosyl derivative **10** by reacting with *p*-TsCl/ pyridine in CH_2Cl_2. Compound **10** was characterized by ^{1}H NMR spectrum from the appearance of Ar-CH_3 protons at δ 2.36 and from the ^{13}C spectrum from the appearance of methyl protons at δ 23.5. Treatment of compound **10** with sodium azide in DMF at 60°C for 6 h gave the required target molecule in 82% yield (**Scheme II**) and was characterized by ^{1}H NMR from the appearance of C-5 azide protons at δ 3.50 (dd, 1H, H-5), 3.39 (dd, 1H, H-5′) and ^{13}C NMR from the appearance of C-5 carbon at δ 52.2. To conclude, the synthesis of target molecule **3** in 5 steps starting from D-ribose has been successfully accomplished.

Experimental Section

Solvents were dried with appropriate drying agents and distilled before use. All reactions were monitored by TLC. Spots were detected under UV light or by charring with 10% H_2SO_4 in ethanol. Solvents were removed under reduced pressure below 40°C. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz and chemical shifts are referenced to TMS (δ 0.0). ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz and ^{13}C chemical shifts are referenced to $CDCl_3$ (δ 77.00).

1-O-Acetyl-2, 3, 5-tri-O-benzoyl-β-D-ribofuranose 4.

D-Ribose (5.0 g, 33.33 mmole) was dissolved in anhydrous pyridine (50 mL) at 95°C. To this solution was added benzoyl chloride (23.5 mL, 200 mmole) at such a rate that the temperature of the rapidly stirred mixture remained below 95°C. After stirring for 1 hr, the reaction mixture was gradually cooled to RT and diluted with dichloromethane (100 mL). This solution



Reagents and conditions: i) TsCl, Py, CH_2Cl_2, 0°C-RT, 10 h; ii) NaN_3, DMF, 60°C, 6 h; iii) DEAD, TPP, DPPA, THF, 0°C-RT, 4 h.

Scheme II

was washed successively with 1*N* HCl, satd. $NaHCO_3$ solution and water. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to a syrup which was subjected to purification by recrystallization from absolute ethanol to obtain the title compound (7.1 g, 35%) as a white solid. m.p. 120-21°C[11]. To a solution of β-D-ribofuranose tetrabenzoate (4.0 g, 7.06 mmol) in acetic anhydride (30 mL) at 0°C was added BF_3-Et_2O (2.14 g, 15.2 mmol) slowly and stirred for 1 h. The reaction mixture was quenched slowly with satd. $NaHCO_3$ solution and extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water, dried (anhyd. Na_2SO_4) and concentrated to a syrupy residue which was purified by column chromatography (hexane:EtOAc, 8:1) to obtain the title compound (1.82 g, 51%) as white solid. m.p. 129-30°C. ^{1}H NMR ($CDCl_3$): δ 8.1 (d, 2H, ArH), 8.06 (d, 2H, ArH), 7.92 (d, 2H, ArH), 7.59-7.31 (m, 9H, ArH), 6.50 (d, 1H, *J*= 2.0 Hz, H-1), 5.95 (dd, *J*=4.0, 4.2Hz, 1H, H-3), 5.83 (d, *J*= 4.0Hz, 1H, H-2), 4.88-4.80 (m, 2H, H-5,5′), 4.59-4.35 (m, 1H, H-4), 2.05 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$): δ 169.4, 166.3, 165.7, 165.4, 134.0, 133.9, 133.6, 130.2, 130.1, 130.0, 129.2, 129.0, 128.9, 128.8(2), 98.8, 80.4, 75.4, 71.8, 64.1, 21.3. Anal. Calcd for $C_{28}H_{24}O_9$: C, 66.66, H, 4.80. Found: C, 66.35, H, 4.72%.

2-(2′, 3′, 5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-4-methyl-1, 2, 3-triazole 6 and 1-(2′, 3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-4-nitro-5-methyl-1, 2, 3-triazole 7 (isomeric mixture).

1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **4** (1.8 g, 3.56 mmole) and 5-nitro-4-methyl-1,2,3-triazole **5** (0.492 mg, 3.84 mmole) were thoroughly mixed in a mortar, then heated in an oil-bath to 130°C when a melt was formed. *p*-toluenesulfonic acid (10 mg) was added and heated *in vacuo* at 130-35°C for 15 min. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with satd. $NaHCO_3$ solution and water. The organic phase was dried over anhyd. Na_2SO_4, filtered and concentrated to a syrupy residue which was purified by column chromatography (hexane:EtOAc, 8:1) to give an inseparable mixture of **6** and **7** (1.4 g, 69%) as an oil. R_f 0.56 (hexane:EtOAc, 4:1). ^{1}H NMR ($CDCl_3$): δ 8.15-7.99 (m, 6H, ArH), 7.63-7.27 (m, 9H, ArH), 6.74 (d, *J*=4.0 Hz, 0.3 H, H-1), 6.48 (d, 0.7H, H-1), 6.34-6.07 (m, 2H, H-2,3), 5.47-4.64 (m, 3H, H-4,5,5′), 2.55, 2.52 (2s, 3H, CH_3-triazole); ^{13}C NMR ($CDCl_3$): δ 166.5, 166.4, 165.8, 165.5, 165.3, 164.8, 151.8, 151.6, 143.5, 142.1, 134.3, 134.1, 133.7, 130.3, 130.2 (2), 130.1, 129.9, 129.1, 129.0, 128.9, 128.8(2), 128.7, 95.1, 92.6, 84.7, 81.9, 75.1, 71.9, 70.7, 64.3, 63.5, 14.5, 11.9.

2-(β-D-Ribofuranosyl)-5-nitro-4-methyl-1, 2, 3-triazole 8 and 1-(β-D-ribofuranosyl)-4-nitro-5-methyl-1, 2, 3-triazole 9.

To a solution of **6** and **7** (1.4 g, 2.48 mmole) in methanol (30 mL) was added NaOMe (1.0 mL, 1*M* solution in methanol). The solution was stirred at RT for 12 hr, then neutralized with acetic acid and concentrated. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 20:1) to obtain **8** (0.403 g, 63%) and **9** (0.152 g, 24%) as colourless oils.

Analytical data for **8**: R_f 0.41 (CH_2Cl_2:MeOH, 10:1). ^{1}H NMR (CD_3OD): δ 5.98 (d, *J*= 3.5Hz, 1 H, H-1), 4.62 (dd, *J*= 4.0, 2.5 Hz, 1H, H-3), 4.43 (dd, *J*=3.5, 3.6 Hz, 1H, H-2), 4.19-4.15 (m, 1H, H-4), 3.80 (dd, *J*= 8.8, 4.5 Hz, 1H, H-5), 3.72 (dd, *J*= 8.8, 4.5

Hz, 1H, H-5′), 2.57 (s, 3H, CH_3-triazole); ^{13}C NMR (CD_3OD): δ 152.8, 143.8, 98.9, 87.9, 76.6, 72.4, 63.7, 12.0. Anal. Calcd for $C_8H_{12}N_4O_6$: C, 36.93, H, 4.65, N, 21.53. Found: C, 36.78, H, 4.59, N, 21.42%.

Analytical data for **9**: R_f 0.40 (CH_2Cl_2:MeOH, 10:1). ^{1}H NMR (CD_3OD): δ 6.30 (d, 1 H, H-1), 4.63 (dd, 1H, H-3), 4.46 (dd, 1H, H-2), 4.17-4.14 (m, 1H, H-4), 3.81 (dd, *J*=8.0, 4.3 Hz, 1H, H-5), 3.70 (dd, *J*=8.0, 4.0 Hz, 1H, H-5′), 2.60 (s, 3H, CH_3-triazole).^{13}C NMR (CD_3OD): δ 152.6, 143.3, 96.8, 90.2, 73.4, 72.0, 63.2, 12.0. Anal. Calcd for $C_8H_{12}N_4O_6$: C, 36.93, H, 4.65, N, 21.53. Found: C, 36.72, H, 4.60, N, 21.31%.

2-(5-O-*p*-Toluenesulfonyl-β-D-ribofuranosyl)-5-nitro-4-methyl-1,2,3-triazole 10.

To a solution of **8** (0.3 g, 1.15 mmole) in CH_2Cl_2 (5 mL) and pyridine (1.0 mL) at 0°C was added *p*-toluenesulfonyl chloride (0.263 g, 1.38 mmole) slowly. The reaction mixture was gradually warmed to RT and stirred for 10 hr before being diluted with CH_2Cl_2 (50 mL). The organic phase was washed successively with a 2% aq. HCl solution (5 mL), satd. aqueous $NaHCO_3$ solution (25 mL) and water (25 mL). The organic layer was separated, dried (anhyd. Na_2SO_4), filtered and concentrated to afford the crude product, which was purified by column chromatography (hexane:EtOAc, 3:1) to give **10** (0.351 g, 75%) as a white crystalline solid, m.p. 116-17°C. R_f 0.45 (hexane:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, ArH), 7.24 (d, 2H, ArH), 5.99 (d, *J*= 3.3 Hz, 1 H, H-1), 4.60-4.01 (m, 5H, H-2, 3, 4, 5, 5′), 3.95-3.60 (br OH), 2.49 (s, 3H, CH_3-triazole), 2.36 (s, 3H, $ArCH_3$); ^{13}C NMR ($CDCl_3$): δ 172.2, 151.4, 146.5, 145.8, 143.1, 142.9, 132.3, 131.9, 130.7, 130.5, 130.4, 130.3, 128.4, 128.2, 127.9, 96.9, 82.1, 74.9, 71.4, 69.4, 23.5, 11.8. Anal. Calcd for $C_{15}H_{18}N_4O_8S$: C, 43.48, H, 4.38, N, 13.52. Found: C, 43.26, H, 4.31, N, 13.41%.

2-(5-Azido-5-deoxy-β-D-ribofuranosyl)-4-methyl-5-nitro-1,2,3-triazole 3.

To a solution of **10** (0.32 g, 0.77 mmole) in *N*,*N*-dimethylformamide (5.0 mL) was added sodium azide (0.075 g, 1.15 mmole) at RT. The reaction mixture was heated to 60°C and stirred for 6 hr, cooled and diluted with CH_2Cl_2 (50 mL). The organic phase was washed with water (25 mL), dried (anhyd. Na_2SO_4), filtered, and concentrated to afford the crude product, which was purified by column chromatography (hexane: EtOAc, 3:1) to give pure **3** (0.181 g, 82%) as a colorless syrup. R_f 0.47 (hexane:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 5.96 (d, *J*= 3.0Hz, 1 H, H-1), 4.54-4.42 (m, 3H, H-2, 3 and OH), 4.19-4.15 (m, 1H, H-4), 3.50 (dd, *J*= 9.0, 4.3 Hz, 1H, H-5), 3.39 (dd, *J*=9.0, 4.1 Hz, 1H, H-5′), 2.52, 3H, CH_3-triazole); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 151.2, 142.5, 97.4, 84.1, 75.0, 71.5, 52.2, 11.7. Anal. Calcd for $C_8H_{11}N_7O_5$: C, 33.69, H, 3.89, N, 34.38. Found: C, 33.45, H, 3.82, N, 33.99%.

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